

Welcome to 4 researchers

FALL 1998

10

Childhood disorders, the role genes play in activating the immune system, and how faulty cell transmission can lead to osteoporosis are some of the research interests of four new investigators at the NHGRI. The findings from their research could lead to results as diverse as discovering the gene that causes attention-deficit disorder to using gene therapy to treat immune deficiency diseases such as AIDS, cancer, and lysosomal storage disorders.

Maximilian Muenke, MD Medical Genetics Branch



Dr. Muenke seeks the genes that direct brain, face, and skull formation. To find these genes, he evaluates people with abnormal craniofacial development. He has studied extensively holoprosencephaly (HPE), the most common structural problem of the forebrain that, in turn, influences the face. The condition appears in one in every 16,000 live births with varying severity. Some forms of HPE are inherited; others arise when the fetus is exposed to certain chemicals. The disease causes mental retardation, cleft lip, missing or improper placement of noses or eyes, and incorrect formation of the front teeth. Muenke and his colleagues found the first gene, known as Sonic Hedgehog, which causes HPE. He suspects that some of the alterations in this gene interfere with the ability to bind cholesterol, an important component for normal brain development. Low cholesterol has been found in some patients to cause HPE. The genetics of attention-deficit hyperactivity

disorder (ADHD) also interest Muenke, who is hunting for ADHD genes in large families where several members are affected.

http://www.nhgri.nih.gov/Intramural_research/People/muenke.html

Fabio Candotti, MD Clinical Gene Therapy Branch



A different gene controls each of the many steps involved in activating the immune system, the body's warrior against invaders. Detrimental alterations in certain genes cause several different—and often fatal—immune deficiency diseases. Dr. Candotti investigates ways to create gene therapy for severe combined immunodeficiencies. Patients with these disorders can have problems with either their B cells (the ones that make antibodies) or T cells (the ones that kill foreign organisms or that stimulate other cells involved in immune responses). These white blood cells, like other blood components, are all formed from the same kind of ancestral cells. Candotti is especially interested in a gene called JAK3 that, when faulty, restricts cell development. He suspects that a well-ordered JAK3 is critical in the molecular signaling that tells the progenitor cell to become a T cell instead of some other blood component. By understanding the mechanism at the root of immune system diseases, Candotti believes that eventually it will be possible to develop ways to correct a faulty genetic code directly.

http://www.nhgri.nih.gov/Intramural_research/People/candotti.html

Pamela Schwartzberg, MD, PhD

Genetics Disease Research Branch



Dr. Schwartzberg studies how cells communicate with each other. Cells receive external signals that tell them to divide or change their properties in other ways. Before any changes can occur, however, those signals must be transmitted to the nucleus. This process, known as signal transduction, is governed by various molecules. If problems occur in the molecules or how they transmit signals, cells can continue dividing, leading to cancer. Or, in other cases, cells could fail to divide and produce key molecules required for normal growth and development. Schwartzberg studies tyrosine kinases, a group of signal-transducing molecules, and their genes. In her work with mouse Src genes, she evaluates how various alterations influence the cell signals that direct bone formation. Certain mutations, for instance, give mice osteopetrosis, a disorder where bones thicken and become brittle. This area of research may lead to new treatments for other bone diseases, including osteoporosis. Schwartzberg's laboratory also investigates failures in other tyrosine kinases that cause immune system disorders.

http://www.nhgri.nih.gov/Intramural_research/People/schwartz.html

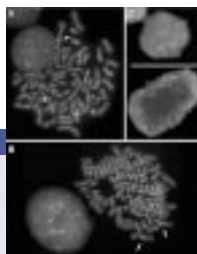
Donna Krasnewich, MD, PhD

Medical Genetics Branch



Dr. Krasnewich studies a rare inherited childhood disorder known as carbohydrate-deficient glycoprotein syndrome (CDGS). Affected children have severe developmental delays, abnormal fat distribution and sexual maturation, along with heart, blood, nerve, vision, and bone problems. Approximately 200 CDGS cases exist world-wide, but Krasnewich expects to see more as doctors learn to properly diagnose the disease. The syndrome got its name in 1986 when researchers realized that several medical problems were caused by faults in the making of certain complex sugars. These N-linked oligosaccharides (or glycans) work in enzymes, blood-clotting agents, cell communication, proteins that hold cells together, embryonic development, and organ functioning. Krasnewich studies the final products of N-glycan synthesis, a production process that may involve 200 steps or more, to learn what can go wrong upstream. Understanding the process and the roles N-linked glycans play in the body may lead not only to treatments for CDGS patients, but to better blood-clotting products as well. ●

http://www.nhgri.nih.gov/Intramural_research/People/krasnewich.html



August, 1997
Gene associated with familial Mediterranean fever identified.



September, 1997
Removal of the Dvl1 gene from mice found to disrupt their normal social behavior.

December, 1997
Mutated gene that causes Pendred syndrome identified using the recently completed physical map of human chromosome 7.

August, 1997
AIB1 gene found to be expressed at abnormally high levels in the tumor cells of breast cancer patients.